



# Molecular profile of metastasis, cell plasticity and EMT in pancreatic cancer: a pre-clinical connection to aggressiveness and drug resistance

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## Abstract

The metastasis is a multistep process in which a small proportion of cancer cells are detached from the colony to enter into blood cells for obtaining a new place for metastasis and proliferation. The metastasis and cell plasticity are considered major causes of cancer-related deaths since they improve the malignancy of cancer cells and provide poor prognosis for patients. Furthermore, enhancement in the aggressiveness of cancer cells has been related to the development of drug resistance. Metastasis of pancreatic cancer (PC) cells has been considered one of the major causes of death in patients and their undesirable prognosis. PC is among the most malignant tumors of the gastrointestinal tract and in addition to lifestyle, smoking, and other factors, genomic changes play a key role in its progression. The stimulation of EMT in PC cells occurs as a result of changes in molecular interaction, and in addition to increasing metastasis, EMT participates in the development of chemoresistance. The epithelial, mesenchymal, and acinar cell plasticity can occur and determines the progression of PC. The major molecular pathways including STAT3, PTEN, PI3K/Akt, and Wnt participate in regulating the metastasis of PC cells. The communication in tumor microenvironment can provide by exosomes in determining PC metastasis. The components of tumor microenvironment including macrophages, neutrophils, and cancer-associated fibroblasts can modulate PC progression and the response of cancer cells to chemotherapy.

**Keywords** Pancreatic cancer · Metastasis · Epithelial-mesenchymal transition · Drug resistance · Cell plasticity

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## 1 Introduction

In Western countries, pancreatic cancer (PC) is suggested to be one of the leading causes (fourth in ranking) of death and by 2030, its mortality rate is suggested to enhance and become the second reason of death, just after lung cancer [1, 2]. In spite of advances in the field of medicine, PC is still among the major causes of death and it is considered as a lethal disease. The drawback of PC is a lack of symptoms in the early stages and major symptoms are revealed when the disease is at advanced stages [3]. There are epidemiological studies about diagnosed cases of PC that in 2018, 458,918 cases were diagnosed which caused 432,242 deaths among patients [4]. Although techniques for diagnosis and management of PC have reached a satisfactory level, the 5-year survival rate of PC is still 9% [4, 5]. The majority of PC cases is pancreatic ductal adenocarcinoma (PDAC) comprising 90% of cases. The risk factors for the development of PC include smoking, alcoholism, diabetes mellitus, obesity, aging, genetic and epigenetic alterations, family history, and others [4, 6]. The prognosis of PC patients is suggested to be low that is because of delays in diagnosis, rapid progression, and the ability of tumor cells in drug resistance development. The clinical symptoms lack in PC patients and therefore, there are challenges in the use of biomarkers including CA19-9 for the diagnosis of patients in terms of sensitivity and specificity [7, 8].

At the early stages of progression, surgical resection is used for the treatment of PC, and even after a successful operation, there is a high chance of recurrence [9]. Significant changes in genetic loci and remarkable mutations occur in PC to provide abnormal expression of tumor-suppressor and tumor-promoting factors, and dysregulation of important biological mechanisms including apoptosis, autophagy, drug resistance, malignancy, and metastasis [10]. The new therapeutics for PC are suggested to be focused on targeting *KRAS* and germline mutations since *KRAS* mutations are among the most common changes in the DNA of PC cells, and at the next rank, are germline changes [11, 12]. *ATM*, *BRAF*, *BRCA1*, *BRCA2*, *CDKN2A*, *FGFR1*, *HER2*, *MET*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PI3CA*, *PMS2*, and *PTEN* are other genes that display abnormal changes in PC progression and they are responsible for drug resistance, malignant progression and other abnormal behaviour of PC cells [13]. More importantly, in 60–70% of PC cases, there are mutations that silence *DKN2A*, *TP53*, and *SMAD4* [14, 15].

The significant advances in the field of biology have resulted in shedding more light on the understanding of genomic and epigenetic changes in the PC. SEMA3C has the ability to increase tumorigenesis in PC cells; Silencing

SEMA3C diminishes cancer formation *in vivo* in the xenograft model. SEMA3C stimulates autophagy in increasing tumorigenesis, and silencing SEMA3C enhances sensitivity to KRAS or MEK1/2 [16]. The expression level of IPO7 enhances in PC; IPO7 escalates metastasis and prevents apoptosis. Silencing IPO7 impairs tumorigenesis and lung metastasis *in vivo*. IPO7 promotes ERBB2 expression in increasing tumorigenesis in PC [17]. The changes in the metabolism of PC cells can be provided by the dysregulation of molecular pathways; UBE2C has the ability to increase EGFR expression to induce PI3K/Akt axis in glycolysis stimulation [18]. COL10A1 binds to the DDR2 receptor on the surface of cells and after that, it stimulates MEK/ERK axis to mediate EMT in increasing liver metastasis of PC cells [19]. Furthermore, HOXA10 enhances NF- $\kappa$ B as a mechanism in enhancing colony formation and improving tumorigenesis in the xenograft model [20]. The epigenetic changes can also mediate carcinogenesis in PC; LINC01234 down-regulation can impair tumorigenesis in PC. LINC01234 sponges miR-513a-3p to elevate H6PD expression (Table 1) [21].

Owing to understanding the molecular dysregulation in increasing tumorigenesis in PC, the current review paper focuses on the role of molecular mechanisms in the metastasis of PC. The focus is on understanding the EMT mechanism and cell plasticity in PC cells. Moreover, the molecular profile of cancer metastasis is highlighted based on the most dysregulated mechanisms and pathways. The association between metastasis and drug resistance is provided. Finally, the bioinformatics analysis of the metastasis profile in PC is provided.

## 2 The concept of metastasis and related mechanisms

Metastasis is considered a factor in providing unfavourable prognosis and death of patients [36]. In metastasis, the cancer cells are detached from their primary site and disseminate into distal and surrounding organs. A few and small proportions of tumor cells have the ability to metastasis and after they metastasize into other tissues, they grow and proliferate [37, 38]. In the process of metastasis, plastic alterations occur in tumor cells and they may demonstrate features of epithelial-mesenchymal transition (EMT) [39, 40]. The metastasis of tumor cells is coordinated by genomic, transcriptome, and proteomic factors. The initial step for metastasis is to invade the surrounding tissues and cross over the endothelial barrier [41]. Metastasis is one of the features and hallmarks of tumor cells and the intrinsic and extrinsic factors in the tumor microenvironment (TME) participate in the invasion of cancer cells. After that, cancer cells have the capacity of entering blood vessels and they cross over

**Table 1** A number of aberrantly expressed genes in PC

Factor	The result on PC cells	Ref
P53 P21	IX is an JNK inhibitor that regulates p53 and p21 in DNA damage induction and mediating G2 arrest	[22]
PAF1 YAP1	The cooperation of PAF1 and YAP1 in metastatic ducts increases PC progression	[23]
-	The increase in glutaminolysis can mediate hypoxia-induced drug resistance	[24]
Wnt/ $\beta$ -catenin/TCF7	Pancreatic stellate cells mediate Wnt in increasing glutamine metabolism and promoting PC proliferation	[25]
ENO1	Immunosuppression activity and enhancement in the proliferation of PC cells	[26]
miR-3960/TFAP2A	The exosomes derived from PC cells are able to increase TFAP2A and Akt expression and reduce PTEN expression in tumorigenesis	[27]
STAT3/GPX4	Thiostrepton is able to suppress STAT3/GPX4 axis in ferroptosis induction	[28]
CD73/cGAS-STING	CD73 suppresses STING and its cooperation with CD39 causes an increase in PC progression	[29]
SF3B1/HIF1	SF3B1 increases HIF1 in PC progression	[30]
-	The polyamine synthesis is supported in PC by the function of ornithine aminotransferase	[31]
STAT3	The STAT3 in cancer fibroblasts is able to mediate immunosuppression	[32]
DDR1	The PC outcome is regulated by the collagenolysis-mediated DDR1	[33]
Myoferlin	Therapeut targeting myoferlin stimulates mitophagy and mediates ferroptosis	[34]
GREM1	The cellular heterogeneity in PC is preserved by GREM1	[35]

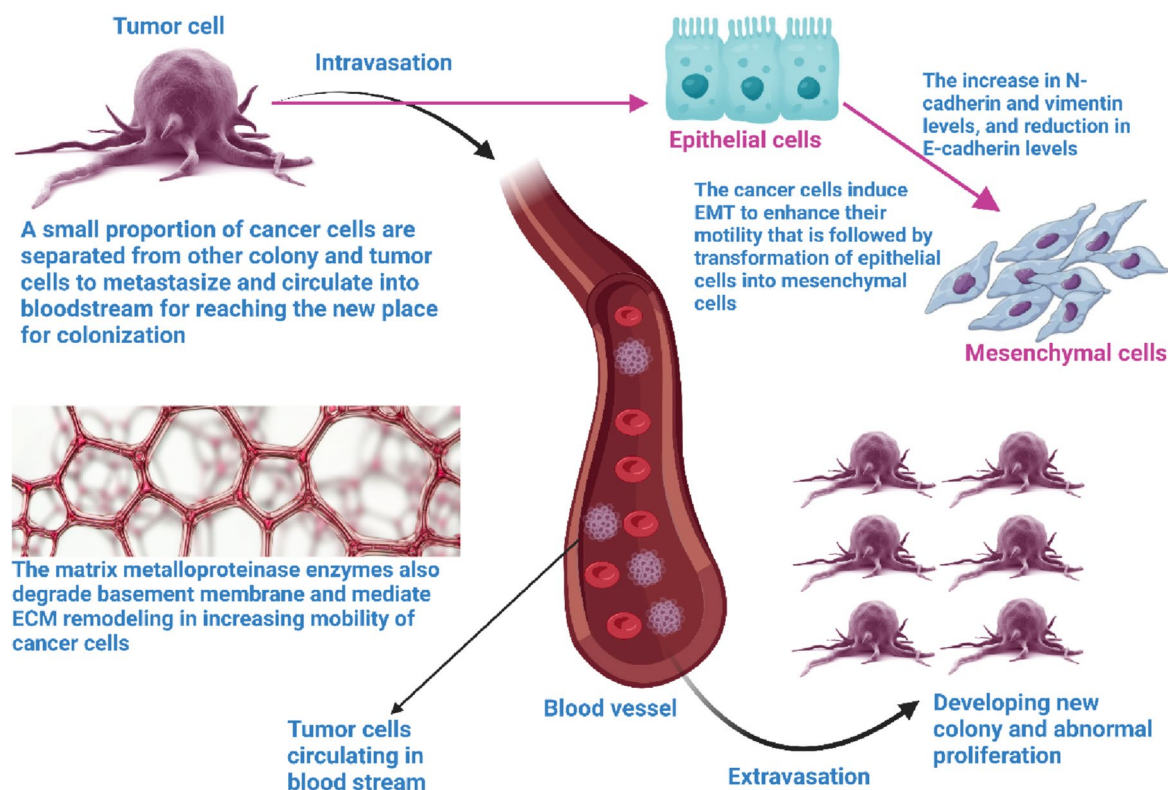
the vascular endothelium called intravasation. The different factors and cell compartments participate in the metastasis and invasion [42–44]. Then, the cancer cells exit the blood vessels to accommodate in a new place, known as extravasation. At the primary site, the cancer cells proliferate to increase their population. The metastasis of cancer cells is coordinated by a number of molecular pathways in cancer. The tumor invasion can be inhibited by function of METTL3 acetylation [45]. The mitochondrial  $m^5C$  can enhance metastasis and dissemination of tumor cells [46]. The cholesterol reprogramming and lymphangiogenesis can be accelerated by FASM to stimulate lymph node metastasis [47]. The transactivation of CDCA3 can be triggered by MYBL2 in escalating invasion of bladder tumor [48]. PRMT5 escalates arginine methylation of MTHFD1 to promote invasion and migration [49]. The inflammation increases metastasis of tumor cells and HECTD3 promotes IKK $\alpha$  activity to induce NF- $\kappa$ B axis [50]. The changes occurring in promoter of pathways can improve metastasis; EZH2 binds to promoter of KRT14 to escalate its expression in increasing peritoneal invasion [51]. Therefore, metastasis of tumor cells is coordinated by various molecular interactions (Fig. 1).

### 3 EMT in pancreatic cancer

#### 3.1 Metastasis

EMT is a mechanism involved in cancer invasion that by changing the transformation of epithelial cells to mesenchymal cells in escalating metastasis and migration of tumor cells. The EMT involves changing the molecular levels

along with phenotypic alterations. The N-cadherin and vimentin levels enhance, while E-cadherin levels reduce to increase the motility of cancer cells. The stimulation of EMT can enhance the invasion of tumor cells and it causes chemoresistance [52–54]. EMT has been considered as a potential mechanism in increasing metastasis of PC cells; the modulation of EMT in tumor cells can be provided by EMT-inducing transcription factors (EMT-TFs) that include Slug, Snail, ZEB proteins, and TGF- $\beta$ . The decrease in glutamine level (depletion) can cause an increase in the invasion of PC cells that is because of Slug upregulation. In fact, loss of glutamine causes stimulation of ATF4 and ERK to enhance Slug expression in EMT induction and escalating invasion and metastasis of PC cells [55]. The upregulation of ZEB1 also participates in an increase in metastasis of PC cells through EMT induction. Musashi2 increases EGF expression to induce EMT and for this purpose, EGF promotes EGFR to increase ZEB1 expression, resulting in ERK/MAPK axis stimulation in escalating PC invasion through EMT induction [56]. The EGF-mediated EMT in PC cells is a potential subject and in addition to musashi2, calreticulin has the ability of EMT induction. The enhancement in the expression level of EGF is based on the function of calreticulin to promote integrin/EGFR and ERK/MAPK pathways in EMT induction [57]. Hence, ERK/MAPK axis is considered a factor in EMT induction and its suppression can prevent metastasis of PC. FAM172A suppresses ERK, vimentin, and MMP-9 levels, while it promotes E-cadherin and  $\beta$ -catenin levels to impair EMT-mediated invasion of PC cells [58]. However, only one mechanism has not been shown for the regulation of MAPK. GINS2 is able to induce ERK/MAPK axis in EMT stimulation and enhance PC invasion



**Fig. 1** The process of metastasis in human cancer. The process of metastasis starts when a small proportion of cancer cells that have high migratory ability, are separated from other tumor cells in the colony to enter into the bloodstream known as intravasation. After circulation, it exists bloodstream, known as extravasation and after

accommodation in new and secondary site, they proliferate and establish new colonies. The EMT induction enhances the invasion of tumor cells and upregulation of matrix metalloproteinase enzymes can result in the degradation of the basement membrane in increasing invasion of tumor cells

and metastasis [59]. Notably, the tumor cells choose a continuum of EMT states and the highest metastatic potential is observed when a late-hybrid EMT state occurs [60]. Another EMT-TF is SNAIL which has the ability of EMT stimulation in accelerating PC invasion. The reason for focusing on EMT-TFs is that they are among the most common modulators of EMT induction and cancer metastasis, and if their related pathways are highlighted, the way for the development of new therapeutics is paved. MACC1 has been shown to positively interact with SNAIL in increasing fibronectin 1 (FN1) and trans-repression of CDH1 in improving PC invasion [61].

Owing to the critical function of EMT in increasing metastasis of PC cells, there has been an effort in EMT regulation. Emodin is an anti-cancer agent in reducing tumorigenesis in PC; emodin promotes miR-1271 expression as a way to down-regulate Twist1 in EMT inhibition and reduce the invasion of PC [62]. Betulinic acid administration is beneficial in reducing the metastasis of PC cells. Upon administration of betulinic acid, stimulation of AMPK occurs to mediate EMT and enhance the stemness of PC cells through upregulation of SOX2, Oct4, and Nanog [63]. When

genomic changes occur in PC cells, the expression level of some of the factors alters. The upregulation of SMARCA4 in PC results in the stimulation of Wnt/ $\beta$ -catenin to induce EMT in escalating PC invasion and metastasis [64]. Calpains2 has shown also potential in upregulation of the Wnt/ $\beta$ -catenin axis to trigger EMT in PC invasion and metastasis [65]. Hence, EMT is considered a mechanism involved in promoting PC invasion (Fig. 2).

### 3.2 Drug resistance association

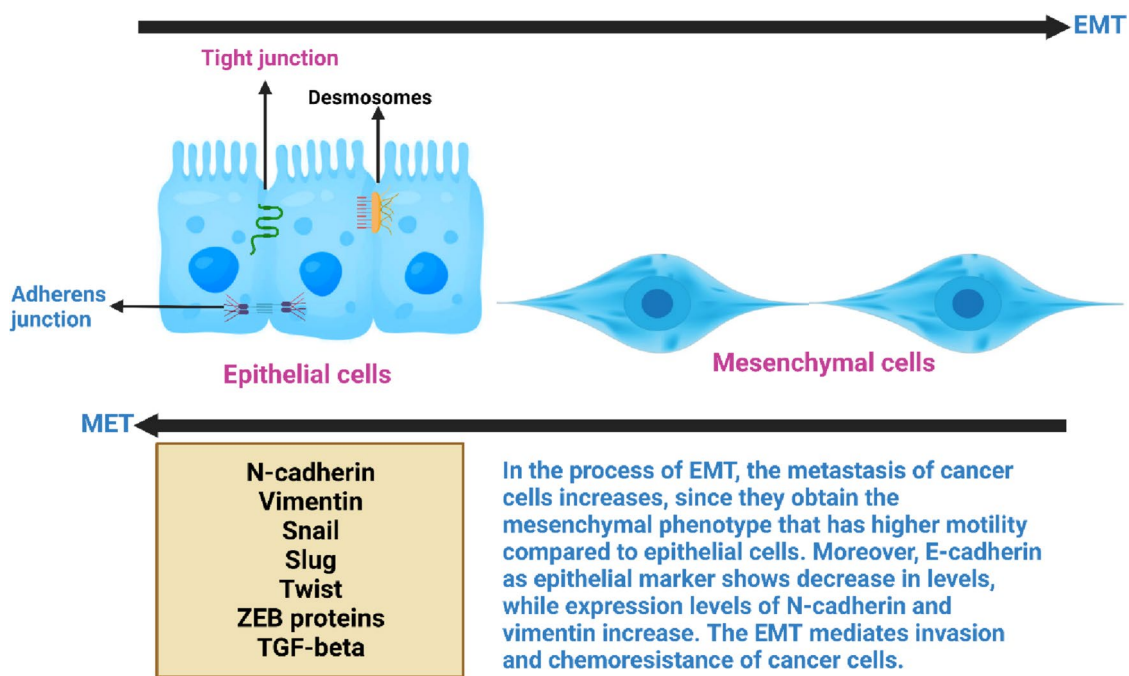
The emergence of drug resistance in PC has been suggested to cause therapy failure in patients at the clinical level. With respect to the fact that enhancement in the aggressiveness potential of PC cells can escalate tumorigenesis and subsequent chemoresistance, there should be an association between metastasis and drug resistance in PC cells. The cisplatin resistance in PC cells can emanate from an increase in metastasis; Par-4 determines the response of PC cells to chemotherapy. Low expression levels of Par-4 in PC cells can develop cisplatin resistance through upregulation of PI3K/Akt to mediate EMT [66]. On the other



hand, a reduction in the expression level of oncogenic factors can cause chemosensitivity. Low expression level of lncRNA NEAT1 in PC cells causes gemcitabine sensitivity. However, when the expression level of NEAT1 increases during tumorigenesis and progresses towards advanced stages, NEAT1 sponges miR-506-3p to escalate ZEB2 expression in EMT induction and enhancing metastasis, resulting in gemcitabine resistance [59]. Therefore, the function of EMT in the development of chemoresistance in PC is critical, and related molecular mechanisms should be highlighted. miR-3656 is capable of enhancing gemcitabine sensitivity in PC and for this purpose, it downregulates RHOA to suppress EMT-mediated gemcitabine resistance. However, the upregulation of TWIST1 can abrogate the function of miR-3656 in increasing drug sensitivity in PC cells [67]. As a result, therapeutics have been directed towards the regulation of EMT in increasing drug sensitivity. It has been reported that the application of oncolytic adenovirus co-expressing decorin and Wnt decoy receptor can participate in suppressing drug resistance in PC through ECM degradation and disruption of EMT [68]. Table 2 and Fig. 3 summarize the function of EMT in PC metastasis and chemoresistance.

### 4 Cell plasticity in pancreatic cancer

Although there are connections between EMT and cell plasticity in human cancers, it would be better to describe the cell plasticity in PC in a separate section to comprehensively discuss the related pathways regulating plasticity in cancer cells and its function in the modulation of invasion and aggressiveness. The KRAS mutation occurs in PC and this tumor-promoting factor is responsible for an increase in cell plasticity and tumor initiation through wild-type PI 3-kinase p110α [95]. The presence of stem cells can promote tumorigenesis in PC. The plasticity of PC stem cells can be escalated by the balance of MYC/PGC-1α balance. The down-regulation of MYC results in PGC-1α upregulation that participates in the oxidative metabolism of cancer stem cells that is abrogated in resistant populations [96]. The PC plasticity increases by CD44 upregulation. The PC cells with high levels of CD44 display cell plasticity, EMT induction, and low response to chemotherapy. The poor expression of CD44 enhances the chemosensitivity of PC cells [97]. In fact, the presence of epithelial plasticity has been shown to escalate



**Fig. 2** A schematic representation of EMT. The mechanism of EMT is suggested to be vital for metastasis and drug resistance development in cancer cells. The tight junctions, adherens junctions, and des-

mosomes are responsible for keeping epithelial cells together so that during EMT, they are lost and mesenchymal cells with high motility are generated

**Table 2** The EMT-mediated increase in cancer metastasis and chemoresistance

Molecular network	Remark	Ref
LAMC2/EMT	LAMC2 increases EMT and ABC transporter function in gemcitabine resistance development	[69]
miR-203a-3p/EMT	miR-203a-3p suppresses EMT	[70]
ATP11A/EMT	ATP11A stimulates EMT through the upregulation of Snail2 and ZEB1	[71]
Circ-0092367/miR-1206/ESRP1/EMT	Circ-0092367 reduces miR-1206 expression to increase ESRP1 expression in EMT suppression	[72]
eIF4A1/c-MYC/miR-9/EMT	eIF4A1 stimulates c-MYC/miR-9 axis to induce EMT	[73]
IQGAP1/Wnt	IQGAP1 stimulates the Wnt axis to mediate EMT	[74]
E-cadherin/EMT	Changes in tumor microenvironment reduce E-cadherin levels to mediate EMT	[75]
FTO/EMT	FTO induces EMT	[76]
MEKK3/TAP-TAZ/EMT	MEKK3 stimulates EMT and increases the stemness of PC cells through promote the recruitment of YAP/TAZ	[77]
IL-6/ERK/NF- $\kappa$ B	Curcumin suppresses EMT and metastasis of PC cells through down-regulation of IL-6/ERK/NF- $\kappa$ B	[78]
Calreticulin/EMT	EMT induction by calreticulin in enhancing tumorigenesis and metastasis	[79]
-	Astaxanthin suppresses EMT and gemcitabine resistance	[80]
-	The stimulation of EMT-mediated gemcitabine resistance in PC is based on loss of equilibrative Nucleoside Transporter 1	[81]
ASIC1/3/RhoA	The ASIC1 and ASIC3 stimulate Ca <sup>2+</sup> /RhoA axis in promoting acidity-mediated EMT	[82]
NUDCD1/EMT	NUDCD1 promotes EMT and reduces apoptosis	[83]
miR-135b-5p/NR3C2	miR-135b-5p is capable of targeting NR3C2 in EMT induction	[84]
-	HS-173 is considered an EMT suppressor that reduces metastasis of PC cells	[85]
XIST/miR-429/ZEB1	XIST promotes ZEB1 expression by miR-429 sponging to induce EMT	[86]
Circ_0001666/miR-1251/SOX1	Circ-0001666 promotes SOX4 expression through miR-1251 sponging in EMT induction	[87]
LASP2/TGF- $\beta$ /EMT	LASP2 disrupts TGF- $\beta$ -induced EMT to impair metastasis	[88]
Iron/EMT	Chronic exposure to iron induces EMT through p53 loss	[89]
FHL3/EMT	FHL3 stimulates EMT	[90]
CCL21/CCR7	CCL21/CCR7 axis stimulates EMT in enhancing PC invasion	[91]
-	Glycolysis results in EMT induction	[92]
GATA6/EMT	GATA6 impairs EMT	[93]
Yap1-2/EMT	Yap1-2 isoform participates in TGF- $\beta$ 1-mediated EMT in PC cells	[94]

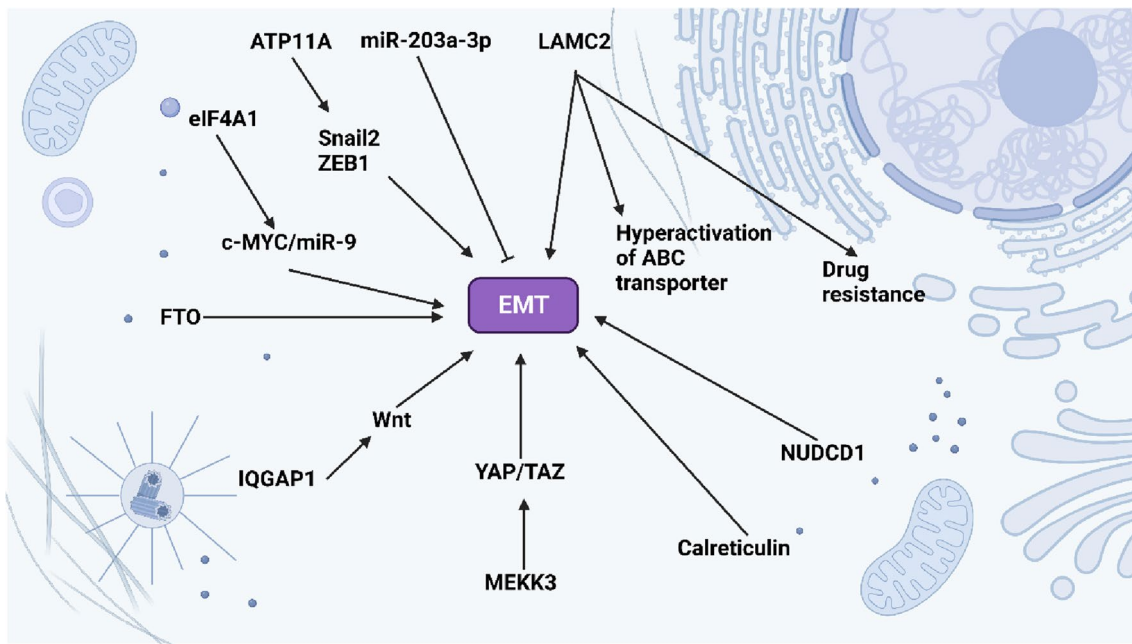
PC invasion and metastasis [98]. However, the epithelial plasticity in PC is under the tight control of molecular interactions. The upregulation of TBK1 can occur by Axl to induce epithelial plasticity in PC [99]. After the identification of such pathways, their blockage can be performed. The application of warfarin can suppress Gas6-induced Axl upregulation to impair epithelial plasticity and invasion of PC cells [100]. Interestingly, Prrx1 has been related to an increase in mesenchymal plasticity of PC cells to enhance aggressiveness [101]. Therefore, both epithelial and mesenchymal plasticity are important factors in the determination of PC invasion and metastasis. In addition to epithelial and mesenchymal plasticity, acinar cell plasticity modulates the metastasis of PC cells. The acinar cell plasticity is facilitated by the function of IL-22 to stimulate PC invasion in mice, and suppression of STAT3 can abrogate this role [102]. Another aspect is the metabolic plasticity of PC cells that promotes G6PD expression in the development of erlotinib resistance in PC cells [103]. The PC plasticity can be accelerated upon

loss of KDM6A that promotes activating A level to induce EMT and p-p38 in driving PDAC invasion [104]. Putting it all together, it appears that the process of cell plasticity in PC is highly controlled [105–109] and even changes in the tumor microenvironment can modulate cell plasticity [110]. Owing to the function of cell plasticity in determining PC invasion, studies have focused on targeting related pathways and mechanisms through the blockage to prevent the invasion of tumor cells [111]. Moreover, cell plasticity is a determining factor for the response of PC cells to immunotherapy [112].

## 5 Molecular profile of metastasis in pancreatic cancer

### 5.1 Non-coding RNAs

The microRNAs (miRNAs) are considered small and short non-coding RNAs with linear structures and a low number



**Fig. 3** The function of EMT in increasing cancer metastasis and drug resistance

of nucleotides that are able to modulate important biological mechanisms in tumor cells, especially PC. The wealth of evidence has highlighted the function of miRNAs in the regulation of metastasis in PC. The invasion of PC cells can be significantly elevated by the function of miR-3613-5p which can be obtained through the reduction in CDK6 and also promotes lymph node metastasis [113]. Notably, miRNAs can exert two functions in PC cells that previous experiment highlighted the oncogenic function, while another study demonstrates that miR-1297 is capable of reducing MTDH expression to impair the invasion and migration of PC cells [114]. One of the most common and dysregulated factors in PC is KRAS in that its function is oncogenic and it displays high expression levels in PC cells and tissues. Interestingly, miR-216 has shown the ability in reducing KRAS expression to suppress metastasis of PC cells and to induce apoptosis [115]. The function of miRNAs in PC is versatile and in addition to metastasis, they can regulate proliferation, apoptosis, and metabolism. However, an interesting experiment has highlighted that when glycolysis-related enzymes are affected by miRNAs, it can affect the metastatic potential of PC cells. miR-489-3p reduces levels of PKM2 and LDHA as glycolytic enzymes to suppress glucose metabolism, growth, and metastasis of PC cells [116].

The long non-coding RNAs (lncRNAs) are an important member of non-coding RNAs lacking protein synthesis, similarity in structure to miRNAs (both of them are linear structures) and their length is more than 200 nts. The lncRNA location can be cytoplasm or nucleus, and they

are potential regulators of molecular pathways, biological mechanisms, and tumorigenesis [117, 118]. The expression level of miRNAs in PC can be reduced by lncRNAs through sponging. lncRNA DANCR has the ability to sponge miR-33b to enhance MMP-16 expression in accelerating invasion and metastasis of PC cells [119]. The expression level of lncRNA AGAP2-AS1 can be increased by the function of RREB1 as an oncogenic factor to reduce levels of ANKRD1 and ANGPTL4 in promoting the growth and metastasis of PC cells [120]. The stability of mRNA can be increased by the function of lncRNA such as the role of lncRNA NEAT1 in enhancing stability of ELF3 at mRNA levels to promote PC invasion and metastasis [121]. The lung tissue is one of the targets of PC cells. When migration and invasion of PC cells enhance, they can metastasize into lung tissue. The lncRNA PLACT1 is able to recruit hnRNPA1 that binds to the  $\text{I}\kappa\text{B}\alpha$  promoter in reducing its expression, resulting in NF- $\kappa\text{B}$  upregulation in promoting PC metastasis [122].

The circular RNAs (circRNAs) are also a member of a large family of non-coding RNAs that can modulate tumorigenesis. The structure of circRNAs is different from other members of non-coding RNAs that they have circle structures and their stability is higher compared to linear structures. The circRNAs can function as modulators of metastasis in PC. Circ-001569 is considered a prognostic factor in PC and it can escalate lymph node metastasis and invasion of PC cells [123]. Similar to lncRNAs, the expression level of miRNAs can be regulated and sponged by circRNAs. The ability of circ-0000284 in the modulation of PC progression has been evaluated and it has been reported

**Table 3** The role of non-coding RNAs in the regulation of metastasis in PC

Non-coding RNA	Remark	Ref
miR-193a-5p	Increase in invasion of PC cells through alternative splicing of OGDHL and ECM1	[126]
miR-202	Suppression of TGF- $\beta$ 1-mediated EMT	[127]
miR-29c	Decrease in miR-29c levels enhances metastasis and stem cell-like phenotype	[128]
miR-200c	DEK down-regulation by miR-200a in reducing invasion	[129]
miR-143	Reduction in metastasis of PC cells	[130]
miR-623	Down-regulation of MMP-1 to reduce tumor invasion	[131]
miR-141	Down-regulation of NRP1 by miR-141 in suppressing invasion	[132]
miR-29b-3p	Methylation of its promoter enhances angiogenesis and invasion	[133]
miR-212	Down-regulation of PTCH1 in increasing cancer invasion	[134]
miR-539	SP1 down-regulation to suppress EMT and invasion	[135]
miR-509-5p and miR-1243	EMT inhibition to increase gemcitabine sensitivity	[136]
LncRNA BX111	Upregulation of BX111 under hypoxia that promotes ZEB1 expression in cancer invasion	[137]
LncRNA TPT1-AS1	Positive association between TPT1-AS1 and ITGB3 enhances invasion and metastasis	[138]
LncRNA AFAP1-AS1	Inhibition of AFAP1-AS1 by oridonin suppresses EMT	[139]
LncRNA TP73-AS1	TP73-AS1 sponges miR-141-3p to increase BDH2 expression in enhancing metastasis	[140]
LncRNA PTTG3P	Enhancement in carcinogenesis and invasion	[141]
LncRNA DLX6-AS1	miR-181b down-regulation to enhance metastasis	[142]
LncRNA GAS5	EMT suppression	[143]
LncRNA MEG3	PI3K down-regulation and suppressing growth and metastasis	[144]
LncRNA SNHG6	miR-218-5p sponging to increase HMGB1 expression in enhancing metastasis	[145]
LncRNA SNHG14	miR-613 sponging to enhance cancer invasion	[146]
LncRNA PWAR6	Epigenetically silencing of YAP1 to enhance metastasis	[147]
LncRNA STXBP5-AS1	Recruitment of EZH2 to regulate ADGB expression in impairing metastasis and drug resistance	[148]
LncRNA H19	Suppression of H19/EMT axis by curcumin	[149]
LncRNA FAM83H-AS1	Increasing stability of FAM83H to upregulate $\beta$ -catenin in increasing tumorigenesis	[150]
LncRNA HOTAIR	miR-613 sponging to increase Notch3 expression in increasing proliferation and metastasis	[151]
LncRNA TP73-AS1	miR-200a sponging in increasing MMP-14 expression	[152]
CircRNA 0075829	Sponging miR-1287-5p to increase LAMTOR3 expression	[153]
CircRNA ADAM9	Sponging miR-217 to enhance PRSS3 expression for tumorigenesis	[154]
CircRNA FGFR1	miR-532-3p sponging to increase PIK3CB levels in promoting invasion and metastasis	[155]

that circ-0000284 reduces miR-1179 expression through sponging to enhance RHPN2 expression in accelerating metastasis and angiogenesis in PC cells [124]. The EMT as an inducer of metastasis in PC cells can be modulated by circRNAs. The expression level of circ-STK39 escalates in PC cells and tissues, and it reduces miR-140-3p expression to enhance TRAM2 levels in EMT induction and facilitates tumorigenesis and invasion of PC cells [125]. Therefore, it can be concluded that metastasis of PC cells is regulated by a variety of molecular mechanisms that are considered downstream targets of non-coding RNAs (Table 3, Fig. 4).

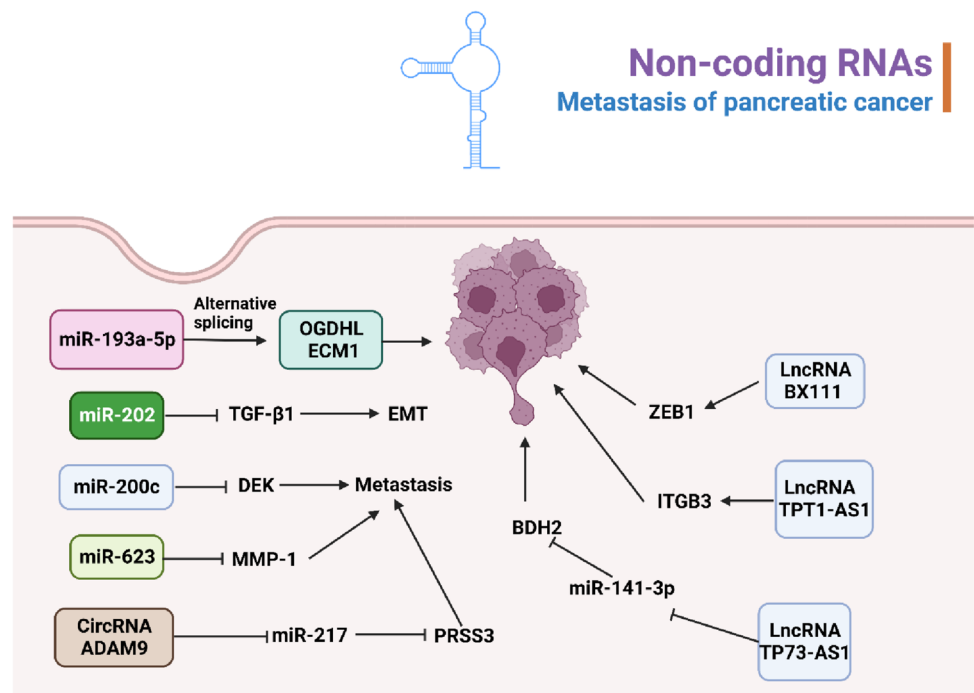
## 5.2 Reactive oxygen species

The changes in levels of reactive oxygen species (ROS) have recently been emerged as a new aspect of regulating tumorigenesis that is because of the versatile function of such free radicals in modulating various biological mechanisms. The

metastasis of PC cells is tightly regulated by levels of ROS. The function of Kras in PC is oncogenic and it promotes invasion and migration of tumor cells. Interestingly, Kras escalates levels of CCL15 to promote ROS and EMT levels. More importantly, ROS can stimulate EMT in enhancing the invasion of PC [156]. When the PC cells are exposed to the pressure of high glucose levels, it can cause enhancement in progression and mediate chemoresistance. High glucose levels are able to enhance ROS generation. NOX4 is required for increasing ROS generation to promote MMP-3 levels in increasing PC invasion and metastasis [157]. Moreover, the expression level of MMO-9 enhances to promote PC invasion. Palmitic acid has been shown to enhance invasion and metastasis of PC cells and to this end, it promotes TLR4 expression to induce ROS overproduction. Then, NF- $\kappa$ B axis induction occurs to enhance MMP-9 levels in escalating PC invasion and metastasis [158]. More importantly, when levels of ROS by antioxidants reduce, the ability of



**Fig. 4** The contribution of non-coding RNAs in the regulation of PC invasion



hypoxia in EMT induction and enhancing tumorigenesis in PC decreases [159].

### 5.3 Chromosomal instability

Although the role of chromosomal instability in the modulation of PC invasion has been ignored, it should be noted that the instability of chromosomes participates in the malignancy of tumor cells. Therefore, this aspect should be evaluated in terms of regulating PC invasion. The chromosomal instability can be accelerated by the function of APOBEC3A and it mediates co-deletions in DNA repair-related pathways to enhance the metastasis of PC cells [160].

### 5.4 STAT3

Another molecular mechanism participating in the regulation of PC metastasis is the STAT3 axis. The levels of STAT3 suppress by IL-37 in impairing metastasis of PC cells. However, the HIF-1 $\alpha$  axis reduces IL-37 levels to induce the STAT3 axis in enhancing lymph node metastasis and invasion of visceral [161]. The expression level of STAT3 in PC is regulated by SOCS5 as an endogenous suppressor. Therefore, if the expression level of SOCS5 reduces, it causes upregulation of STAT3. miR-301a contributes to the downregulation of SOCS5 to induce JAK/STAT3 axis in escalating metastasis of PC cells [162]. Owing to the function of STAT3 in enhancing metastasis of PC cells, its downregulation by RNAi can impair angiogenesis and progression [163]. Moreover, phosphorylation of STAT3 at Tyr705 can

cause progression and metastasis of PC cells [164]. Hence, the small molecule inhibitors of STAT3 based on targeting these sites have been developed. It has been reported that WB436B is a small molecule that can suppress the phosphorylation of STAT3 at Tyr705 to impair the invasion of PC *in vivo* [165]. The silencing of STAT3 can disrupt the invasion of PC cells and reduces MMP-7 expression [166]. There is an association between STAT3 and cell plasticity. When the expression level of STAT3 enhances by NETO2 in PC cells, it causes EMT induction to promote invasion and metastasis [167]. An important inducer of STAT3 in addition to JAK2, is IL-6. The upregulation of STAT3 in PC can occur by IL-6 in promoting invasion of PC. HIC1 is capable of suppressing the IL-6/STAT3 axis to diminish levels of its downstream targets including c-Myc, VEGF, CyclinD1, MMP-2, and MMP-9 in suppressing metastasis of PC cells [168]. Therefore, STAT3 is a regulator of PC metastasis which is summarized in Table 4.

### 5.5 HIF-1 $\alpha$

Hypoxia is considered another factor in the progression of PC; the expression level of HIF-1 $\alpha$  enhances as a response to hypoxia and by binding to promote lncRNA CF129, it diminishes CF129 expression to increase metastasis and invasion of PC cells through upregulation of FOXC2 [184]. The carcinogenesis in PC increases by the function of hypoxia. There is positive feedback and interaction between lncRNA ZEB1-AS1 and HIF-1 $\alpha$  in which HIF-1 $\alpha$  increases ZEB1-AS1 expression in promoting ZEB1 expression and

**Table 4** The role of STAT3 in the regulation of PC metastasis

Pathway	Remark	Ref
STAT3/NF- $\kappa$ B	Suppression of the NF- $\kappa$ B axis through STAT3 down-regulation impairs invasion and growth	[169]
USP5/STAT3	USP5 promotes STAT3 expression in increasing metastasis of PC	[170]
IL-32 $\alpha$ /JAK2/STAT3	IL-32 $\alpha$ suppresses the JAK2/STAT3 axis in suppressing metastasis and EMT	[171]
BRM/miR-302a-3p/SOCS5/STAT3	BRM increases miR-302a-3p expression to increase STAT3 expression through SOCS5 down-regulation	[172]
-	The extracellular vesical ezrin derived from PC cells can stimulate the STAT3 axis to increase invasion	[173]
ciRS-7/miR-7/EGFR/STAT3	ciRS-7 reduces miR-7 expression to induce EGFR/STAT3 axis	[174]
-	Fraxetin prevents the STAT3 axis to suppress metastasis and increases the potential of gemcitabine in cancer therapy	[175]
-	The cooperation of ZEB1 and IL-6/11-STAT3 axis participates in increasing metastasis and invasion of PC cells	[176]
AMPK/STAT3/NF- $\kappa$ B	The invasion of PC cells is suppressed by the function of solasodine through AMPK upregulation to suppress STAT3/NF- $\kappa$ B	[177]
miR-155/SOCS1/STAT3	miR-155 promotes STAT3 expression through SOCS1 down-regulation	[178]
miR-130b/STAT3	miR-130b reduces STAT3 expression to suppress metastasis	[179]
-	STAT3 stimulates metastasis and angiogenesis	[180]
Smad4/STAT3	Smad4 suppresses STAT3 phosphorylation to impair metastasis	[181]
Gp130/STAT3	Gp130 increases STAT3 expression to enhance the aggression of PC cells	[182]
STAT33/Nrf2/EMT	STAT3/Nrf2 axis stimulates EMT	[183]

escalating metastasis of PC cells [185]. Interestingly, the function of HIF-1 $\alpha$  in the regulation of epigenetic factors can determine the invasion of PC cells. HIF-1 $\alpha$  undergoes upregulation under hypoxia and it enhances miR-646 expression to down-regulate MIIP in enhancing tumorigenesis. MIIP is able to impair the deacetylase ability of histone deacetylase 6 (HDAC6) to induce acetylation and degradation of HIF-1 $\alpha$  [186]. HIF-1 $\alpha$  enhances miR-212 expression as a mechanism to develop lymph node metastasis and invasion of PC cells [187]. The progression of PC cells can occur as a response to the autocrine loop. HIF-1 $\alpha$  promotes VEGF expression and then, VEGF mediates the interaction of NRP-2 and integrin- $\alpha$  $\beta$  to stimulate FAK/ERK axis in

enhancing HIF-1 $\alpha$  expression. Therefore, such a positive feedback loop enhances metastasis and progression of PC cells [188]. The involvement of HIF-1 $\alpha$  in the regulation of PC invasion has been mentioned in both *in vitro* and *in vivo*, and when the stability of HIF-1 $\alpha$  reduces, the progression of PC decreases [189]. The increase in acetylation of HIF-1 $\alpha$  reduces its expression. However, when deacetylation of HIF-1 $\alpha$  is mediated by lncRNA MTA2R, it causes accumulation of HIF-1 $\alpha$  in enhancing carcinogenesis [190]. Notably, an increase in Snail expression can be stimulated by HIF-1 $\alpha$  in enhancing tumorigenesis and invasion of PC cells [191]. Hence, the upregulation of HIF-1 $\alpha$  can be considered a factor in enhancing the metastasis of PC cells.

**Table 5** The involvement of PTEN/PI3K/Akt axis in the regulation of PC metastasis

Molecular pathway	Remark	Ref
PTEN	Upregulation of PTEN increases radio-sensitivity	[199]
IGF-1/PTEN/PI3K/Akt	IGF-1 reduces PTEN expression to induce PI3K/Akt axis	[200]
miR-132/PTEN	The PTEN down-regulation by miR-132 in enhancing progression and metastasis	[201]
CASC2/miR-21/PTEN	CASC2 enhances PTEN expression through miR-21 suppression in inhibiting invasion	[202]
ITGA6/RPSA/PI3K	The cooperation of ITGA6 and RPSA results in the upregulation of PI3K t enhance metastasis	[203]
miR-139-5p/PI3K/Akt	miR-139-5p suppresses invasion of PC cells through PI3K/Akt down-regulation	[204]
PI3K/Akt/NF- $\kappa$ B	Curcumin suppresses EMT through down-regulation of PI3K/Akt/NF- $\kappa$ B	[205]
PI3K/Akt/mTOR/PGAM1	The PI3K/Akt/mTOR axis increases PGAM1 expression to enhance the invasion and migration of PC cells	[206]

## 5.6 PTEN/PI3K/Akt

Dysregulation of PTEN/PI3K/Akt axis has been well-documented in PC (Table 5) and it should be noted that PTEN has anti-cancer activity, while PI3K/Akt has oncogenic function. The expression level of PTEN reduces in PC patients and it causes lymph node metastasis of tumor cells. PTEN promotes FOXO3a expression to upregulate PLZF, resulting in VEGF down-regulation in preventing the progression and invasion of PC cells [192]. However, the expression level of PTEN reduces by miR-32-5p in increasing metastasis. LncRNA GAS5 promotes PTEN expression through miR-32-5p sponging in reducing invasion and metastasis of PC cells [193]. There are regions on PTEN that miRNAs can bind to them. miR-92a-3p diminishes PTEN expression to enhance the growth and invasion of PC cells [194]. GFR $\alpha$ 2 has also the potential in promoting miR-17-5p expression to down-regulate PTEN in promoting the progression and perineural metastasis of PC cells [195]. On the other hand, the function of PI3K/Akt in PC is tumorigenic; interestingly, the invasion of PC stem cells can be increased by PI3K/Akt. BMI-1 has the ability of stimulation of PI3K/Akt to enhance metastasis [196]. The overexpression of GLP-1R has been suggested to prevent PC invasion and that is because of PI3K/Akt suppression by GLP-1R [197]. Although irradiation has been considered a major tool in PC therapy, this therapeutic tool can accelerate the invasion and metastasis of tumor cells. Upon exposure to carbon ion irradiation, nitric oxide obtains the ability to stimulate the PI3K/Akt axis to enhance the metastasis of PC cells [198].

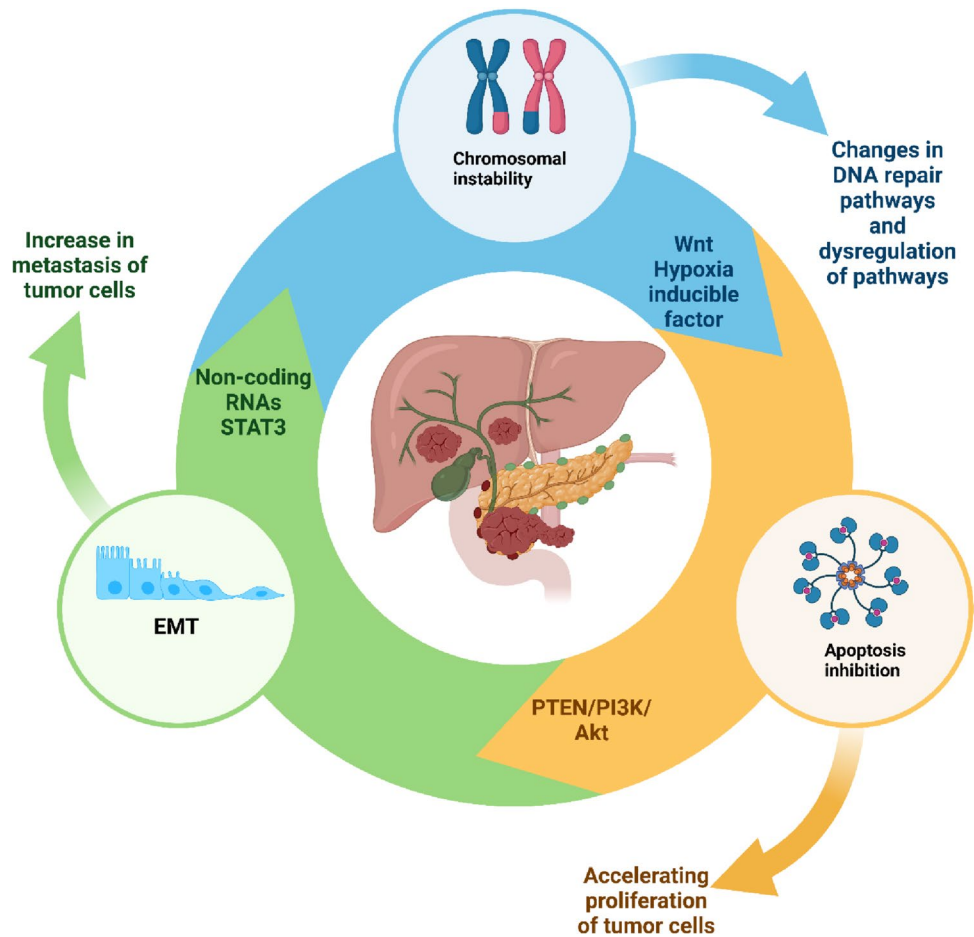
## 5.7 Wnt/ $\beta$ -catenin

The abnormal expression of Wnt has been well-documented in human cancers, particularly PC. This aberrant expression has been shown to modulate hallmarks of PC that metastasis is among them. The acceleration in PC invasion can be performed by Wnt. The expression level of Wnt enhances by function WTAPP1 function to induce metastasis [207]. Both angiogenesis and metastasis increase by the function of Wnt in increasing carcinogenesis in PC [208]. The reduction in the expression level of Wnt disrupts the invasion and metastasis of PC cells. It has been reported that linc00261 sponges miR-552-5p to increase FOXO3 expression, leading to Wnt down-regulation to disrupt invasion [209]. Interestingly, upregulation in Wnt can cause EMT in increasing cancer metastasis, and CDH13 suppresses Wnt/ $\beta$ -catenin to prevent EMT-mediated invasion of PC cells [210]. The stroma of PC is dense and comprised of CAFs, immune cells, endothelial cells, and ECM [211, 212]. The extracellular collagen and matrix can be deposited by the function of CAFs and cause fibrous desmoplasia in enhancing tumorigenesis [213, 214]. Such desmoplastic reactions cause chemoresistance, immune evasion, carcinogenesis, and metastasis [215, 216]. The pancreatic stellate cells (PSCs) are precursors of CAFs in PC and they can be stimulated by PC cells to be activated from a quiescent phenotype into an active myofibroblast phenotype to generate carcinogenic ligands and proteins of ECM [217–219]. The growth factors and cytokines can be secreted by the surrounding stroma of PC to enhance tumorigenesis in PC. The PSCs are able to secrete Wnt and tenascin C ligands in the stimulation of  $\beta$ -catenin and YAP/TAZ pathways in enhancing progression and metastasis [220]. Owing to the function of Wnt in increasing tumorigenesis

**Table 6** The involvement of Wnt in the regulation of PC metastasis and tumorigenesis

Molecular pathway	Remark	Ref
-	The post-transcriptional modifications and changes of $\beta$ -catenin and LRP-6 suppress Wnt	[224]
Wnt2/Wnt	Wnt2 enhances Wnt expression to elevate metastasis	[225]
NMIIA/Wnt	NMIIA increases Wnt and induces EMT in cancer metastasis	[226]
ATDC/Wnt	ATDC stimulates Wnt signalling and promotes $\beta$ -catenin stabilization in enhancing tumorigenesis in PC	[227]
miR-148a/Wnt	miR-148a reduces Wnt expression to suppress PC invasion	[228]
HIF-2 $\alpha$ /Wnt	HIF-2 $\alpha$ displays crosstalk with Wnt in enhancing tumorigenesis	[229]
LINC01133/Wnt	LINC01133 increases Wnt expression in increasing growth and invasion	[230]
BANCR/miR-195-5p/Wnt	BANCR sponges miR-195-5p to enhance Wnt expression	[231]
CISD2/Wnt/EMT	CISD2 enhances Wnt expression to induce EMT	[232]
Wnt/EMT	Vitamin C suppresses Wnt/EMT	[233]
miR-455-3p/Wnt	miR-455-3p inhibits the Wnt axis in reducing cancer progression	[234]
DLX6-AS1/miR-497-5p/Wnt	DLX6-AS1 increases Wnt expression through miR-497-5p sponging	[235]
-	Blockage of the SDF-1/CXCR4 axis suppresses Wnt in reducing tumorigenesis	[236]
LRRFIP1/Wnt/EM<T	Silencing LRRFIP1 suppresses Wnt in EMT inhibition and reducing cancer metastasis and invasion	[237]

**Fig. 5** The role of molecular pathways in the regulation of PC metastasis



in human cancers, studies have focused on the modulation of Wnt in suppressing metastasis. When oridonin is utilized in the treatment of PC, it can inhibit Wnt/ $\beta$ -catenin in impairing EMT and reducing invasion and metastasis of tumor cells [221]. The expression level of Wnt increases by the function of FOXM1 in enhancing the invasion of PC cells, while Merlin suppresses FOXM1/Wnt axis in reducing metastasis [222]. The upregulation of GPX2 in PC cells can cause stimulation of the Wnt axis in the induction of EMT and enhance invasion and migration [223]. Therefore, Wnt is a regulator of PC metastasis, summarized in Table 6. Fig. 5 summarizes the role of molecular pathways in the regulation of PC metastasis.

## 6 Exosomes in pancreatic cancer metastasis

Exosomes are considered biocompatible nanostructures with a size of less than 100 nm that has been surrounded by bilayer membranes and can be loaded with bioactive components including proteins, lipids, nucleic acids, and RNA molecules [238]. The function of exosomes in recent years in tumorigenesis has been of importance in that their

role in reducing/enhancing carcinogenesis can be related to the cargo that they carry [239]. The metastasis of PC cells is highly regulated by exosomes. The enrichment of circ-IARS can be found in exosomes and through modulation of endothelial monolayer permeability, they accelerate the invasion of PC cells [240]. The exosomes can be secreted by almost all the eukaryotic cells. The PC cells are able to secrete exosomes in favour of promoting their invasion and generation of the liver pre-metastatic niche [241]. The exosomes derived from PC cells can affect molecular interactions in tumorigenesis. These exosomes escalate the expression level of TFAP2A, Bcl-2, and p-AKT/AKT, and down-regulate PTEN and BAX levels to prevent apoptosis in increasing tumorigenesis in PC and they also enhance invasion of tumor cells [27]. The application of exosomes as diagnostic factors is extremely increasing due to the capacity of their isolation from the serum of patients. The exosomes can be isolated from the serum of patients and such exosomes are considered as factors involved in EMT induction and escalating cancer metastasis [242]. Interestingly, prometastatic secretome trafficking can be facilitated by exosomes in enhancing the pulmonary invasion of PC cells [243]. Important actions can be performed by exosomes



in the regulation of cancer invasion. The degradation and remodelling of ECM can be induced by exosomes at the primary site and they invade through the basement membrane. They can enter and exist in the vascular system, known as intravasation and extravasation, respectively [243]. The PC cells are not the only source for the secretion and isolation of exosomes in the regulation of tumor metastasis. There are exosomes in the ascites of PC patients that can mediate EndMT in increasing vascular permeability and promoting remote metastasis [244]. Even lymphangiogenesis is accelerated by a critical function of exosomes. The exosomes derived from PC cells can participate in the downregulation of ABHD11-AS1 to increase lymphangiogenesis [245]. Another source for exosomes is mesenchymal stem cells (MSCs) that delivery of miR-124 by such exosomes can impair metastasis and EMT in PC cells, while upregulation of EZH2 abrogates the function of such exosomes [246]. Hence, exosomes are critical regulators of PC metastasis summarized in Table 7.

## 7 Tumor microenvironment components and pancreatic cancer invasion

### 7.1 Macrophages and metastasis

The tumor microenvironment (TME) components participate in the regulation of tumorigenesis and macrophages as immune cells are among such components [260, 261]. The tumor-associated macrophages (TAMs) are capable of secretion of cytokines and inflammatory factors to provide optimal conditions for carcinogenesis [262, 263]. The macrophages can be found in two polarization types including

M1 and M2 macrophages [264]. The identification of M1 macrophages is based on the expression of iNOS and can be developed in response to LPS or IFN- $\gamma$  [265]. The M2 macrophages are anti-inflammatory factors in contrast to M1 polarized macrophages that are developed in response to IL-4 or IL-13, and they can escalate angiogenesis and matrix remodelling [266, 267]. The M1 polarized macrophages exert anti-cancer activity, while M2 macrophages enhance carcinogenesis [268]. The macrophages are able to regulate the metastasis potential of PC cells. Interestingly, The extracellular vesical Ezrin can be derived from PC cells and they stimulate M2 polarization of macrophages in enhancing metastasis of tumor cells [269]. The ability of macrophages is higher than their polarization status and based on their secretion, they can affect the progression and metastasis of PC cells. It has been reported that granulin can be secreted by macrophages and through triggering liver fibrosis, it promotes invasion and migration of PC cells [270]. Furthermore, M2-polarized macrophages are capable of secreting CCL20 to stimulate EMT in escalating invasion and metastasis of PC cells [271]. Interestingly, when PI3K $\alpha$  is genetically suppressed, the number of CD206-positive macrophages reduces which impairs the invasion of PC cells [272], confirming the role of macrophages as potential regulators of metastasis of PC. In addition, pharmacological suppression of macrophages can disrupt the metastasis of PC cells [273]. Interestingly, the chemotherapy response of PC cells can be improved by the polarization of macrophages. UTMD is able to enhance the polarization of macrophages from M2 to M1, and they normalize vasculature in impairing invasion and metastasis of PC cells [274]. Therefore, the communications in the TME can modulate the polarization of macrophages in affecting PC invasion. The ANXA1 can

**Table 7** A summary of exosomes in the regulation of metastasis in PC

Remark	Ref
The exosomes enriched in EphA2 increase cancer invasion and are considered as diagnostic tools	[247]
The PC-derived exosomes transfer Lin28B protein in increasing distant metastasis	[248]
Exosomes derived from PC cells increase EMT through TGF- $\beta$	[249]
Exosomal miR-301a stimulates M2 polarization of macrophages in enhancing cancer metastasis	[250]
Exosomal miR-30b-5p down-regulates GJA1 expression to induce angiogenesis	[251]
Exosomal miR-485-3p modulates PAK1 expression to suppress invasion	[252]
Exosomal miRNAs derived from hypoxic pancreatic stellate cells are able to increase metastasis of PC cells through PTEN down-regulation to induce Akt signalling	[253]
Exosomal miR-222 derived from PC cells increases tumor progression through p27 down-regulation	[254]
Exosomal linc-ROR is able to enhance the interaction of cancer cells and adipocytes in enhancing EMT	[255]
Exosomal miR-125b-5p has the ability to increase metastasis of PC cells	[256]
Exosomal lncRNA-SOX2ot stimulates EMT in increasing PC invasion	[137]
Exosomal delivery of CD44v6/C1QBP complex enhances liver metastasis of PC cells	[257]
M2 polarization of macrophages by exosomal FGD5-AS1 to induce metastasis	[258]
Involvement of exosomes derived from PC cells in the generation of a pre-metastatic niche	[259]

**Table 8** The role of macrophages in enhancing cancer metastasis

Molecular pathway	Remark	Ref
Circ-0018909/miR-545-3p/FASN	Circ-0018909 increases FASN expression through miR-545-3p sponging to increase M2 polarization	[276]
-	Infiltration of M2-polarized macrophages increases lymphangiogenesis	[277]
EGFR/AKT/CREB	REG4 secreted by PC cells stimulates Akt/CREB axis to promote M2 polarization of macrophages	[278]
-	The circuit between macrophages and tumor cells increases cancer invasion	[279]
TNFSF9/Akt/IL-1 $\beta$	TNFSF9 stimulates Akt/IL-1 $\beta$ to promote M2 polarization of macrophages	[280]
-	Increase in inflammation and TAMs promotes the invasion of PC cells	[281]
NLRP3	NLRP3 upregulation in TAMs promotes lung metastasis of PC cells	[282]
-	Tumor-educated macrophages enhance peritoneal metastasis	[283]
-	Glycolysis in tumor-conditioned macrophages escalates invasion	[284]
EMT	M2 polarized macrophages stimulate EMT	[285]

be enriched in extracellular vesicles to stimulate M2 polarization of macrophages and then, such macrophages stimulate endothelial cells and fibroblasts in mediating angiogenesis and matrix degradation [275]. Therefore, macrophages are considered as regulators of metastasis of PC cells (Table 8).

## 7.2 Neutrophils and metastasis

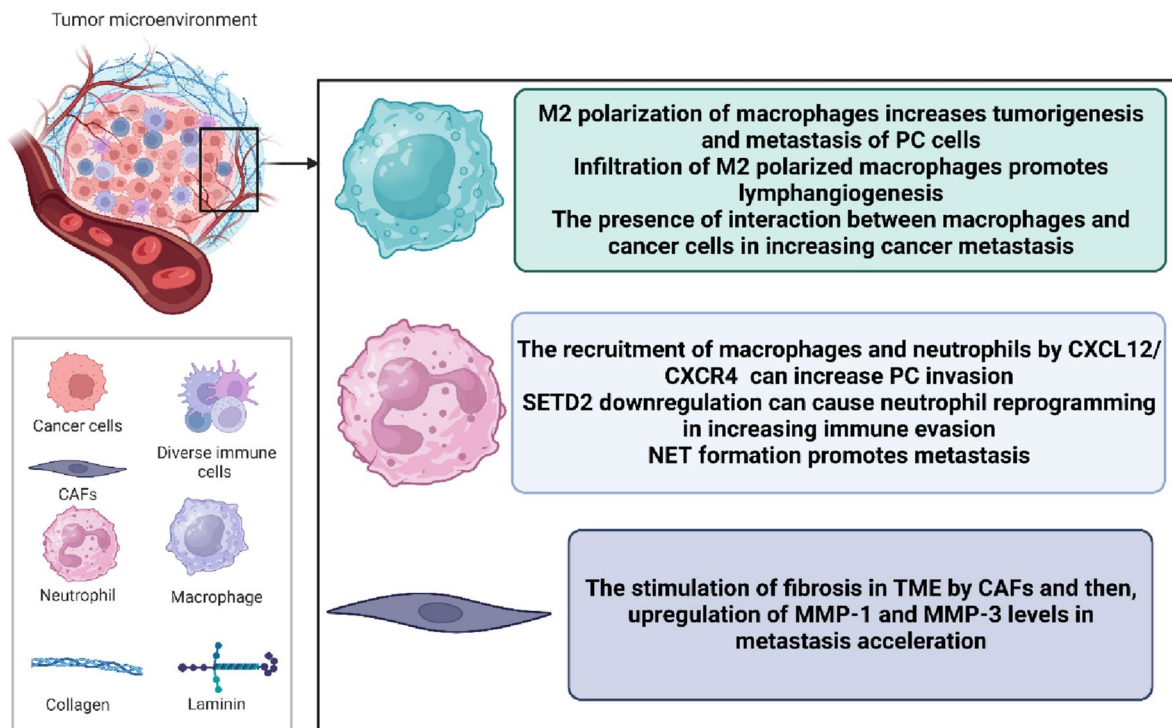
In addition to macrophages, neutrophils play a significant role in the regulation of metastasis and progression of PC cells. The stimulation of NF- $\kappa$ B can occur by upregulation of SPRY1 to mediate CXCL12/CXCR4 axis in neutrophil and macrophage recruitment to promote tumorigenesis in PC [286]. Moreover, the neutrophil reprogramming upon loss of SETD2 causes immune escape in PC [287]. Therefore, tumor-associated neutrophils (TANs) are involved in the modulation of carcinogenesis. The neutrophils are able to suppress microbial attacks and prevent their spread through the production of reactive oxidants, stimulation of granular constituents, and neutrophil extracellular traps (NETs) [288]. There is a wealth of evidence that the presence of NETs can provide the function of TANs in increasing tumorigenesis [289]. Interestingly, the generation of NETs can be accelerated by the function of DDR1 in enhancing the invasion and migration of PC cells [290]. Therefore, if NETs are therapeutically targeted, the invasion potential of PC cells reduces. The HMGB1 derived from NETs is able to increase tumorigenesis. The extravasation can be increased by NETs in promoting liver metastasis. Notably, thrombomodulin is able to mediate degradation of HMGB1 to suppress NETs in impairing metastasis of PC cells [291]. More importantly, the DNA derived from NETs can stimulate pancreatic stellate cells in enhancing progression of PC cells [292]. Sometimes, the potential of NETs in increasing tumorigenesis and metastasis of PC is related to their impact on the other members of tumor microenvironment such as cancer-associated fibroblasts (CAFs). The CAF stimulation by NETs

can increase metastasis of PC cells to liver tissue [293]. Moreover, when PC cells are exposed to chemotherapy, the infiltration of neutrophils enhances that by stimulation of Gas6/AXL axis, it causes increase in metastasis of PC cells [294]. The ability of TANs in secretion of cytokines including TNF- $\alpha$  and TGF- $\beta$ 1 can escalate the liver metastasis of PC cells [295].

## 7.3 Cancer-associated fibroblasts and metastasis

Another member of TME is cancer-associated fibroblasts (CAFs) that their function in increasing the invasion of PC cells has been well-documented. The stimulation of CAFs can occur by ACLP to mediate fibrosis in TME. ACLP enhances levels of MMP-1 and MMP-3 in CAFs to enhance PC invasion [296]. Moreover, by upregulation of PERK, CAFs have the ability to obtain endothelial cell-like phenotype to stimulate angiogenesis in promoting tumorigenesis in PC [297]. The upregulation of FAK in CAFs can improve the metastatic potential of PC cells. The suppression of FAK impairs metastasis and invasion of CAFs and diminishes the amount and level of ECM by CAFs in reducing PC invasion [298]. In fact, the crosstalk between CAFs and tumor cells in TME can determine the aggressiveness and metastasis potential of PC cells [299]. The changes in the shape of CAFs in TME can affect the metastasis of PC cells. The TGF- $\beta$  exposure promotes stiffness, elongation, spread, lamellipodia generation, and spheroid invasion of CAFs that are induced by the function of Rac, RhoA, and ROCK upon exposure to TGF- $\beta$  [300]. Furthermore, an increase in the generation of invadopodia in CAFs by paladin can increase the metastasis of PC cells [301]. The metabolic changes including upregulation of LDH and PKM2 mediated by CAFs can escalate the metastatic potential of PC cells [302]. Hence, if CAFs are therapeutically targeted, the metastatic potential of PC cells reduces. Curcumin is able to suppress CAFs in EMT inhibition and reduce the metastasis of PC

## Tumor microenvironment components in pancreatic cancer metastasis



**Fig. 6** The contribution of TME components in the regulation of metastasis in PC

cells [303]. Exposure to chemotherapy can also induce the activation of CAFs. When exposure to nab-paclitaxel occurs, it causes overexpression of CCL26 in CAFs to stimulate the PI3K/Akt/mTOR axis in enhancing metastasis of PC cells [304]. Therefore, the shape of CAFs, their involvement in the regulation of metabolism, EMT modulation, and secretion of different factors can participate in the regulation of metastasis in PC (Fig. 6).

## 8 Therapeutic modulation of metastasis in pancreatic cancer

The therapeutic compounds have been extensively utilized for disrupting the invasion and metastasis of PC cells. Owing to the function of metastasis in increasing aggressiveness and mediating chemoresistance in PC, therapeutic modulation of metastasis can participate in tumor therapy. The modulation of citrate metabolism in PC cells by berberine can suppress the biosynthesis of fatty acids impairing invasion and metastasis [305]. One of the targets in which PC cells can metastasize is lung tissue. The potential of berberine in suppressing PC invasion can be related to the downregulation of TGFBR1 *in vitro* and *in vivo* [306]. A variety of pathways and mechanisms participate in an increase in

metastasis and progression of PC cells. Upon down-regulation of HDAC, (-)-epigallocatechin 3-gallate (EGCG) stimulates RKIP to enhance histone H3 expression. Then, down-regulation of Snail, NF- $\kappa$ B, MMP-2, and MMP-9 occurs to reduce the invasion of PC cells [307]. The dysregulation of NF- $\kappa$ B can participate in EMT induction and enhancement in the progression of PC cells. However, curcumin as anti-cancer drugs, suppresses the NF- $\kappa$ B axis through down-regulation of IL-6/ERK to suppress EMT and metastasis of PC cells [78]. The potential of curcumin in reducing invasion can be accelerated by loading in nanostructures. The chitosan/PEG-blended PLGA nanostructures can be loaded with curcumin in suppressing metastasis and inducing apoptosis in PC cells [308].

The synergistic regulation of PC metastasis can be provided by a combination of pharmacological compounds. A mixture of quercetin and resveratrol can be utilized to suppress EMT through N-cadherin down-regulation [309]. The modulation of EMT in PC can be performed by regulation of NF- $\kappa$ B. Resveratrol is able to reduce levels of PI3K/Akt in suppression of NF- $\kappa$ B to inhibit EMT in reducing PC invasion and metastasis [310]. Quercetin is also a pharmacological and therapeutic compound in the regulation of EMT in PC therapy. The administration of quercetin can suppress EMT in PC cells through the downregulation of

STAT3 to impair metastasis [311]. The down-regulation of SHH and TGF- $\beta$ /Smad axis can be occurred by quercetin in suppressing metastasis of PC cells [312]. Sulforaphane as another anti-cancer compound has the ability to reduce vimentin, Twist-1, and ZEB1 levels to impair EMT-mediated metastasis of PC cells [313]. The growth factors such as bFGF participate in increasing the invasion of PC cells, while quercetin-3-O-glucoside is able to impair the metastasis of PC cells mediated by growth factors [314]. When there is a loss of SMAD4, the metastasis of PC cells enhances due to overexpression of HNF4G in that this axis is suppressed by the function of metformin [315]. Upon down-regulation of ADAM8 by propofol, reductions in levels of MMP-2, MMP-9, ERK1/2, and integrin  $\beta$ 1 occur to impair metastasis and progression of PC cells [316]. Therefore, EMT, MMPs, and other factors involved in the metastasis of PC cells are modulated by therapeutic compounds in reducing tumorigenesis and aggressiveness.

## 9 Clinical insight and implications

The metastasis of PC and the related therapeutics have been exploited in clinical for the treatment of patients. A phase I/II study has shown the potential of Parenteral Ascorbate at high concentrations for the reduction in proliferation and metastasis of PC, while its toxicity is partial [317]. Although gemcitabine is a good choice in the treatment of patients, the application of paclitaxel through the intraperitoneal route has been shown in phase I/II study to be beneficial in peritoneal metastasis of PC with good tolerability of the drug [318]. However, the problem related to the clinical studies is the low number of participants [319], and therefore, for having a good insight towards the clinical application of drugs in minimizing metastasis, it is suggested to enhance the number of patients. Regardless of treatment, the whole-body FDG-PET is suggested to be beneficial in the detection of metastasis in PC patients [320]. Furthermore, when pharmacoangiographic computed tomography is performed, angiotensin-II can be utilized for the identification of liver metastasis in PC [321]. At the clinical level, when surgical resection of PC is performed, there is a chance of liver metastasis, and therefore, intra-arterial adjuvant chemotherapy is suggested for its prevention [322]. The vaccination has been developed as a new way for the treatment of metastasis in PC and vaccination with HLA-A2 restricted peptide derived from the universal tumor antigen survival could result in a decrease in metastasis of PC cells to the liver [323].

## 10 Conclusion and remarks

The ability of PC cells in metastasis has been a problem at both pre-clinical and clinical levels. The gene analysis displays that dysregulation of molecular pathways and mechanisms significantly participates in the progression of PC cells. The invasion of PC cells does not rely on a single pathway or mechanism, and it has been reported that a variety and complicated molecular mechanisms participate in this mechanism. The aim of the current review was not to only focus on the mechanism of PC cell invasion but also to provide a concept that how metastasis of PC cells enhances and what is the association between this metastasis and chemoresistance development. In the first concept, cell plasticity (mesenchymal and epithelial plasticity) and EMT determine the metastasis of PC cells. The enhancement of PC invasion is mediated by EMT induction and based on the pieces of evidence, EMT-mediated enhancement in aggression of PC cells can stimulate drug resistance. The non-coding RNA transcripts, STAT3, Wnt/ $\beta$ -catenin, and PTEN/PI3K/Akt, are among the most common mechanisms participating in PC progression and metastasis. Therefore, novel therapeutic mechanisms can participate in targeting such pathways for preventing the invasion of PC cells. However, the metastasis of PC cells is more than single participation of pathways and the factors involved in cell-cell communication such as exosomes and the components of TME including macrophages, neutrophils, and CAFs can determine the metastasis of PC cells. The therapeutic modulation of PC metastasis with natural products, small molecules, and nanostructures has been performed to impair tumorigenesis. However, it appears that current studies lack providing a complicated and rational connection between metastasis and drug resistance in PC. In fact, it is obvious that EMT and an increase in metastasis can mediate chemoresistance. However, most of the studies have focused on only understanding the metastasis-related pathways without focusing on therapy response. Therefore, complicated and comprehensive studies in the future are required to reveal and highlight the function of molecular pathways in the regulation of metastasis-related chemoresistance in PC.

There are several perspectives for future papers. For instance, in the case of EMT and metastasis of PC cells, the main emphasis has been on its regulation by upstream mediators, and among all the factors, non-coding RNA transcripts have been critically investigated. However, researchers should focus on the discovery of new proteins related to EMT that have not been investigated before. In the case of EMT, it has been clearly demonstrated that EMT has a close relationship with chemoresistance, but



in other cases, the association with drug resistance has not been completely shown and therefore, studies should perform better and more detailed experiments in understanding the role of metastasis in development of chemoresistance in PC. For instance, the TME has various cells and components, critically regulates tumorigenesis and metastasis of PC cells and although the studies have shown the contribution of TME components in enhancement in progression and invasion, more focus should be directed on TME component-mediated metastasis and drug resistance in PC cells.

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**Data Availability** This is a review article and no data has been used.

## Declarations

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**Informed consent** Not applicable.

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